REMARKS

Upon entry of these amendments, claims 1-11 will be pending in this application. Claims 12-53 have been cancelled without prejudice or disclaimer, as being drawn to a non-elected invention. Claim 1 has been amended herein to more precisely define the claimed invention. Specifically, claim 1 has been amended to recite a method of diagnosing Alzheimer's Disease or "a predisposition thereto." Support for this amendment is found at least at page 2, lines 22 of the specification. Support for the term "preferentially binds" in amended claim 1 can be found at least at page 2, line 7 of the specification. Amended claim 1 also specifies that the amyloid protein is "located in an ocular tissue" and that the detectably labeled compound is an "amyloidophilic fluorescent dye" that is allowed to "distribute into the lens". Support for these amendments can be found at least at page 10, lines 1-3 and 17-20 and at page 14, lines 7-9 of the specification. Finally, amended claim 1 also specifies the step of imaging the ocular tissue. Support for this amendment is found at least at page 5, lines 4-5 of the specification. Claims 2, 3, 6, and 7 have been amended herein to more precisely define the claimed invention and to insure proper antecedent basis for all claim terms.

Accordingly, no new matter has been added herein.

Claim Rejections--35 U.S.C. § 112

Claims 1 and 4-11 have been rejected under 35 U.S.C. § 112, first paragraph for lack of enablement and overbreadth. The Examiner further indicates that it would require undue experimentation to determine which fluorescent dyes can be used as detectably-labeled compounds in accordance with the claims methods. (*See* Office Action at page 2). Applicants traverse.

As noted above, independent claim 1 has been amended herein to more precisely define the claimed invention. Specifically, amended claim 1 now specifies that the detectably-labeled compound that preferentially binds to an amyloid protein in an ocular tissue is an amyloidophilic fluorescent dye. Applicants submit that amended claim 1 is fully enabled by the as-filed specification.

Applicants submit that consideration of each of the *Wands* factors would lead to the conclusion that the skilled artisan would be able to practice the claimed invention without undue experimentation.

Nature of the Invention

Claims 1-11, as amended herein, are drawn to methods of diagnosing Alzheimer's Disease or a predisposition thereto in a mammal by contacting an ocular tissue with a detectably-labeled, amyloidophilic fluorescent dye that preferentially binds to an amyloid protein; allowing the compound to distribute into the lens; and imaging the ocular tissue.

State of the Art

The Examiner has indicated that "the state of art concerning the use of detectably-labeled compounds such as fluorescent dye [*sic.*] to bind to an amyloid protein is not well recognized as there are numerous detectably-labeled compounds which binds to an amyloid-protein and quantitating the level of association of the compound with amyloid protein. . . [I]t is beyond the skilled artisan today to get a detectably-labeled compound such as a radioactively labeled fluorescent dye to be an effective against amyloid protein, which indicates that said mammal is suffering from or is at risk of developing Alzheimer's disease." (Office Action at pages 3-4). Applicants disagree.

The claims, as amended herein, do not recite the use of a radioactively labeled fluorescent dye. Rather, independent claim 1 (and, thus, dependent claims 2-11) specifies the use of a detectably-labeled compound that preferentially binds to an amyloid protein located in an ocular tissue, wherein the compound is an amyloidophilic fluorescent dye. As noted in the instant specification, amyloidophilic dyes that bind to amyloid fibrils are known in the art. (*See, e.g.*, specification at page 14, lines 5-18). Therefore, contrary to the Examiner's contention, Applicants submit that the skilled artisan would be able to select a suitable amyloidophilic fluorescent dye for use according to the claimed methods in order to diagnose Alzheimer's Disease (or a predisposition thereto) in a mammal.

Relative Skill of Those in the Art

Applicants agree with the Examiner that the relative skill of those in the relevant art is high. As such, a skilled artisan armed with the extensive disclosure provided by the specification

as well as the existing knowledge in the art would have little or no difficulty practicing the invention, as now claimed.

Predictability or Unpredictability of the Art

The Examiner has indicated that the art pertaining to diagnosing Alzheimer's disease using detectably-labeled compounds such as fluorescent dye is highly unpredictable. (*See* Office Action at page 4). Applicants disagree.

As indicated in the instant specification, Chrysamine-based probes that specifically bind to Aβ and other fragments of APP (as opposed to those probes that bind to β-pleated sheet protein structures in the eye) are preferred for use in accordance with the claimed methods. (*See* specification at page 14, lines 10-14). Such probes are amyloidophilic fluorescent dyes, and several suitable examples of such probes are provided (*see*, specification at page 14, lines 5-18). Thus, based on this disclosure (as well as the level of knowledge of those skilled in the art), Applicants contend that those skilled in the art would be able to select an appropriate detectably-labeled compound for use according to the claimed method.

Breadth of the Claims

As amended herein, the claims are directed to the use of a detectably-labeled compound that preferentially binds to an amyloid protein in an ocular tissue, wherein the detectably-labeled compound is an amyloidophilic fluorescent dye. Thus, these claims now recite the use of a specific category of detectably-labeled compounds for use in the claimed methods. Therefore, Applicants submit that this claimed use, as amended herein, is commensurate in scope with the disclosure of the instant specification.

Amount of Direction or Guidance Presented

The instant specification provides guidance regarding the use of fluorescent detection techniques in conjunction with the methods of the claimed invention. For example, the specification details how to select suitable amyloidophilic fluorescent dyes (*see e.g.*, specification at page 14, lines 9-21 and page 15, lines 17-20) as well as how to perform fluorescence assays in order to detect compound binding (*see, e.g.,* specification at page 14, line 22 through page 15, line 16). This extensive description provides ample direction or guidance to enable a skilled artisan to carry out the claimed diagnostic methods with little or no difficulty.

Presence or Absence of Working Examples

The specification also contains several working examples which describe how to perform the claimed diagnostic methods. Specifically, Examples 1 and 3 describe Alzheimer's Disease-associated cataract formation in eye tissue, while Example 2 profiles these Alzheimer's Disease associated cataracts. Moreover, Example 4 describes the use of fluorophotometric techniques to diagnose Alzheimer's Disease in human and veterinary patients.

Quantity of Experimentation Necessary

The claimed diagnostic methods, as amended herein, recite three specific, straightforward steps, which can easily be performed by skilled artisan in light of the extensive guidance provided by the instant disclosure as well as the high level of skill in the art.

Specifically, the skilled artisan would be able easily contact an ocular tissue with a detectably-labeled compound that preferentially binds to an amyloid protein. (*See* claim 1(a)). Likewise, those skilled in the art would comprehend (and also be able to practice) the step of allowing the compound to distribute into the lens. (*See* claim 1(b)). In fact, the specification provides describes exactly how each of these steps can be can be accomplished. (*See, e.g.*, specification at page 12, lines 3-15). Moreover, those skilled in the art would also be able image ocular tissue using standard scanning fluorophotometric techniques. (*See,* specification at page 14, lines 22 and 28-29). Finally, specification provides explicit guidance as well as specific examples of suitable amyloidophilc fluorescent dyes. Thus, those skilled in the art would also be able to select and use an appropriate dye in accordance with the claimed diagnostic methods. (*See* specification at page 14, lines 5-18).

Therefore, Applicants submit that only routine experimentation would be required by the ordinarily skilled artisan in order to practice the methods claimed herein.

Thus, when considered together as a whole, Applicants submit that these *Wands* factors support the conclusion that those skilled in the art would be able to practice the claimed methods without undue experimentation. Therefore, claims 1-11, as amended herein, are fully enabled by the as-filed specification. As such, this rejection has been overcome and should be withdrawn.

Claim Rejections–35 U.S.C. § 103

The Examiner has rejected claims 1-11 under 35 U.S.C. § 103(a) as being unpatentable over US2002/0133019 ("Klunk") in view of US Patent No. 5,571,671 ("Potter"). According to the Examiner, while Klunk discloses methods of using thioflavin derivatives in the diagnosis and treatment of patients having diseases associated with an accumulation of neuritic plaques, Klunk fails to disclose the use of these thioflavin derivatives as detectably-labeled compounds that bind to ocular tissue. (*See* Office Action at page 7). However, the Examiner contends that it would have been obvious to one of ordinary skill in the art to modify the thioflavin derivatives disclosed in Klunk in view of the teachings of Potter. (*See* Office Action at pages 7-8). Applicants traverse.

As noted above, claim 1 has been amended herein to recite a method of diagnosing Alzheimer's Disease or a predisposition thereto by contacting ocular tissue with a detectably-labeled compound that preferentially binds to an amyloid protein in the ocular tissue, wherein the detectably-labeled compound is an amyloidophilic fluorescent dye; allowing the compound to distribute into the lens; and imaging the ocular tissue, wherein an increase in binding compared to a normal control level of binding indicates that the mammal is suffering from or is at risk of developing Alzheimer's Disease. There is no teaching or suggestion in Klunk of the use of one of the thioflavin derivatives disclosed therein in the eye. Specifically, Klunk does not teach or suggest that ocular tissue is contacted with the thioflavin derivative, that the thioflavin derivative is allowed to distribute into the lens, and/or that ocular tissue is imaged in order to assess binding of the thioflavin derivative to amyloid proteins located in the ocular tissue. In fact, the Klunk reference is limited to the detection of amyloid deposits in brain tissue. No other tissue types are described or suggested.

Ocular tissue, as required by the claims as amended herein, is structurally and functionally distinct from brain tissue, *e.g.*, brain parenchyma. For example, brain tissue is highly lipophilic in nature, whereas the eye (*e.g.*, the cornea, aqueous humor, and lens) is comprised of alternating hydrophilic and hydrophobic layers. Given the lack of similarity between these two tissue types, one of skill in the art would not be inclined or motivated to apply the compounds of the Klunk reference to the eye. Thus, Klunk does not teach or suggest all of the limitations of the claimed invention.

The addition of the teachings of Potter does not cure these deficiencies, as Potter fails to describe detection of amyloid protein altogether. Rather, Potter describes counting

chromosomes, *i.e.*, detection of trisomy of chromosome 21. While Potter does suggest the examination of "brain--glial, endothelial cells of the meningeal and cortical vessels, and the olfactory epithelium--and possibly of skin fibroblasts" (col. 7, lines 54-56), no mention is made of ocular tissue.

Thus, neither Klunk nor Potter (either alone or in combination) describes or suggests contacting ocular tissue, as now recited in claim 1, as amended herein. Therefore, Applicants submit that this claim is not obvious in view of these references. As such, this rejection should be withdrawn.

Moreover, claims 2-11 each depend (directly or indirectly) on claim 1. As such, they necessarily contain all of the limitations of claim 1, as amended herein. Therefore, for the reasons articulated above, Applicants submit that dependent claims 2-11 are also not obvious over Klunk in view of Potter. Thus, this rejection of these claims should also be withdrawn.

Double Patenting

Claims 1 and 4-11 have been rejected for obviousness-type double patenting in view of claim 1 and 7-16 of US Patent No. 6,849,249. In response, Applicants submit herewith a terminal disclaimer along with the appropriate fee. As such, this rejection has been overcome and should be withdrawn.

CONCLUSION

Applicants submit that this paper is fully responsive and that the application is in condition for allowance. Such action is respectfully requested. Should any questions or issues arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

IABeattie

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